LARA Quarterly Progress Report: 4/01/2023-06/30/2023
2022 Veteran Marijuana Research Grant

Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD

Hilary A. Marusak, PhD, Co-Principal Investigator
Eric A. Woodcock, PhD, Co-Principal Investigator

Project Aims:

This study, referred to here as the 'Neuroimaging Study,' is a supplement (add-on) to our ongoing VMR study (Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health", PIs: Lundahl and Ledgerwood), which will be referred to as the 'Parent Study'. **The Neuroimaging Study will be the first-ever neuroimaging study of cannabis treatment in US armed forces veterans with PTSD, or in any population.** The Parent Study involves randomizing 200 Michigan veterans with PTSD into one of four different THC (∆9-tetrahydrocannabinol) : CBD (cannabidiol) dose conditions (High THC:High CBD; HighTHC:Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. For this Neuroimaging Study, half of the 200 participants from the Parent Study (N=100; 25 of the 50 participants in each dose condition) will additionally complete two brain imaging assessments: one before (i.e., 'baseline' scan) and one after the 12-week treatment period (i.e., 'post-treatment' scan). **Primary outcomes include:** A) neuroinflammatory state as measured via positron emission tomography (PET) imaging with the radiotracer, α-[^{11}C]methyl-L-tryptophan (AMT); B) resting or 'basal' neural network communication as measured via functional magnetic resonance imaging (fMRI); and C) brain activation during well-validated inhibitory control (Go/No-Go) and emotion regulation (Emotional Stroop) tasks as measured via fMRI. We will focus on brain regions that are consistently linked to both PTSD symptom severity and suicidal ideation, and that are densely populated with cannabinoid receptors (which are modulated by acute cannabis/cannabinoid administration). Further, the collection of whole-brain, multi-modal neuroimaging data (structural MRI, functional MRI, and PET imaging data) during the same session will allow us to explore the impact of cannabis/cannabinoid administration on the relationship between neuroinflammatory state and neural network activation and interactions throughout the brain, and link these brain metrics to clinical outcomes (e.g., reduction in suicidal ideation or PTSD/depression symptoms over time). This highly innovative approach will provide unprecedented insight into the neurobiological underpinnings of PTSD and suicidal ideation and the potential therapeutic effects of cannabis (and associated brain mechanisms) on these and other critical outcomes (e.g., quality of life, depressive symptoms). Findings from this Neuroimaging Study may also identify veterans who will benefit most from cannabinoid therapeutics and specific THC:CBD dose combinations therein, and thus, may inform a personalized medicine approach for veterans with PTSD in the future.

1. Project Milestones

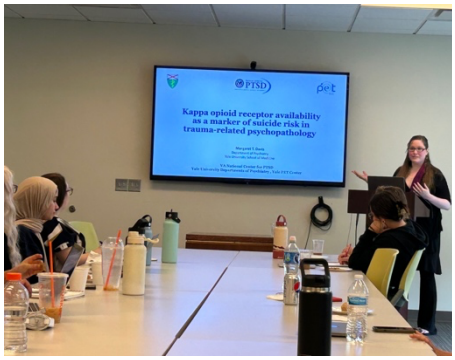
• Percent (%) completion of the project objectives

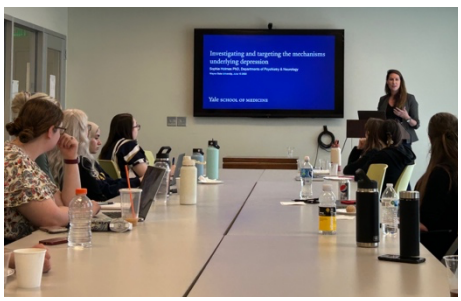
Preparation for Neuroimaging Study Launch: 80%
Neuroimaging Study Progress: 0%
Neuroimaging Study Analyses/Findings Communication: 0%

• Project Progress – Brief outline of the work accomplished during the reporting period and the work to be completed during the subsequent reporting period(s).

Since April, we have continued to refine our protocols and procedures to prepare for study launch. In particular, we have performed another test MRI scan on a human subject and have submitted the finalized MRI protocol to the Wayne State University (WSU) MRI Research Committee for review. We just received approval. In addition, our computer scientist/research technician is continuing to develop data management procedures and data analysis pipeline that are scripted using computer code (python and unix), and performing a full analysis of test MRI data collected using the MR protocol. Our computer scientist/research technician and an undergraduate honors neuroscience student are working to develop automated tools using machine learning and independent components analysis to (1) obtain rapid quality control metrics, and (2) reduce the potential impact of artifact, noise (e.g., head motion, respiration), and signal dropout on MRI data. Preliminary analyses from these projects were presented and disseminated to other researchers at the annual meeting of the Michigan Society for Neuroscience on June 9, 2023 at Michigan State University.

Since the last progress report, we received and installed a backup CO_2 device for our ultra-low temperature freezer, which will maintain freezer temperature in the event of a power outage. We have also purchased and in the processing of installing and testing a temperature sensor to alert the research team if the temperature inside the freezer is too high, thus compromising study samples. We have also made upgrades to our neuroimaging data archiving and processing server.





On June 15, 2023, two PET imaging experts, Drs. Sophie Holmes and Maggie Davis of Yale University, visited our laboratory at WSU to consult on the PET imaging methods and full protocol for this study. Drs. Holmes and Davis gave seminars on the most up-to-date PET imaging methods to the study of psychiatric illness: “Investigating and targeting the mechanisms underlying depression” and “Kappa opioid receptor availability as a marker of suicide risk in trauma-related psychopathology”, respectively. These lectures were open to the WSU community, and drew attendees from several departments, colleges, and

institutes across campus. We also provided a luncheon with the speakers for trainees, including Translational Neuroscience PhD students, postbacc researchers, and postdoctoral trainees. During the on-site visit, Drs. Holmes and Davis reviewed our PET safety protocol and advised on study methods, data analysis processing pipelines, and statistical methods.

In the last progress report, we noted that the MRI and PET imaging centers have purchased new scanners that will be installed in Fall/Winter 2023/2024. Since April, we have learned that the new MRI scanner, a state-of-the-art Siemens MAGNETOM Cima.X 3 Tesla research scanner, will be installed at the WSU Eugene Applebaum College of Pharmacy and Health Sciences—a 5-minute walk from our laboratory space in the Tolan Park Medical Buliding—by May 2024. Construction on the building is expected to begin this summer (2023). At the PET center, the new state-of-the-art Siemens Vision 600 PET/CT system is anticipated to be installed by Fall 2023. Therefore, during the next quarter, we plan to submit the PET scanning protocol to the PET Center's Radioactive Drug Research Committee (RDRC) for review/approval. Once approved, the study protocol will be added to WSU's existing FDA IND for this radiopharmaceutical (i.e., PET tracer) and submitted for FDA and WSU IRB approval.

Since the last progress report, we have also interviewed and are in the process of hiring a part-time (0.5 FTE) research assistant to assist with data collection, participant scheduling and communications, administering participant payments, coordinating with the parent study, and other administrative duties related the Neuroimaging study visits. During this next reporting period, the research assistant will be fully onboarded and trained, including: (1) completing all human subjects training through the Collaborative Institutional Training Initiative (CITI Program), as mandated by the IRB, (2) added to the IRB protocol for this study, (3) shadowing MRI and PET scan visits for other ongoing studies, (4) reviewing study protocols, procedures, and documents (e.g., consent forms), (5) complete MR safety training with Co-PI Marusak, (6) obtain an identification badge from the Detroit Medical Center (DMC), which houses our current MR scanner and the PET camera, and (7) assist the Principal Investigators with testing and finalizing the study protocols and procedures, including establishing standard operating procedures to ensure rigorous and reproducible research.

We have continued to coordinate closely with the Parent Study team, including regular meetings and coordinating the protocol and IRB submissions. Prior to study launch, a full run-through of the non-MRI and non-PET related laboratory procedures and staff training will be conducted. Once complete, we will be ready to begin enrollment once the Parent Study commences. Of note, in effort to conserve expenses for latter years of the study, we are keeping effort on this project, including Principal Investigator effort, low.

• Noteworthy Accomplishments – Identify and describe any milestones reached or noteworthy accomplishments completed during the period.

Trainees on this project presented at the annual meeting of the Michigan Society for Neuroscience:

1. Almaat, A., Narra, A., Tamimi, R., Marusak, H.A. (2023). Extracting neuroimaging quality metrics using MRIQC. 53rd annual Michigan Society for Neuroscience conference, Lansing, MI.

2. Tamimi, R., Zundel, C.G., Ely, S., Evanski, J., Gowatch, L., Bhogal, A., Carpenter, C., Woodcock, E., Marusak, H.A. (2023). Minimizing artifact with multi-echo fMRI data acquisition and processing: An example in a study of children and adolescents. 53rd annual Michigan Society for Neuroscience conference, Lansing, MI.

3. Delays – Brief description of problems or delays, real or anticipated, which should be brought to the attention of the Grant Administrator.

None.

4. Statement concerning any significant deviation from previously agreed-upon Statement of Work.

None.

• Attachments and Other Materials – Provide project materials developed and implemented during the reporting period (e.g. newspaper articles, newspaper advertisements, forms, brochures, announcements, studies, reports, analyses, audits, etc.).”

None.

5. Financial expenditures of grant money and other contributions to the project, in-kind and/or direct funding.

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CATEGORY	TOTAL BUDGET	EXPENSES (THROUGH 6/30/2023)	% OF BUDGET SPENT
Personnel/Fringe	$2,182,687.00	$112,327.33	
Equipment	$42,000.00	$36,143.00	
Supplies/Other	$966,334.00	$4,133.86	
Computers	$12,000.00	$5,093.00	
Consultants	$12,000.00	$855.60	
Travel	-	-	
DIRECT TOTALS	**$3,215,021.00**	**$158,532.79**	
Indirect Costs - 10%	$321,502.00	$15,953.23	
BUDGET TOTALS	**$3,536,523.00**	**$174,386.07**	**4.9%**

Respectfully submitted,

Hilary A. Marusak, Ph.D.
Co-Principal Investigator

Eric A. Woodcock, Ph.D.
Co-Principal Investigator

July 10, 2023

WAYNE STATE UNIVERSITY

Sponsored Program Administration
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FINANCIAL STATEMENT

Agency	WSU Index No.	Report Period			Date
State of Michigan Department of Licensing and Regulatory Affairs Marijuana Regulatory Agency (LARA)	370821	04/01/23	Thru	06/30/23	07/10/23
Title: Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD	**Grant Code** 23T47	**Fund Code:** 23T471 / Org. Code: 06CMM		**Project Period** 09/01/22 Thru 08/31/27	
Principal Investigator Dr. Hilary Marusak	**Final** No	**Report No.** 4		**Grant/Contract No.** VMR2022-02	

CATEGORY	EXPENDITURES		AGREEMENT	
	Current Period	Cumulative	Budget	Balance
Salaries & Wages	$ 30,133.39	$ 87,477.51	$ 1,690,654.00	$ 1,603,176.49
Fringe Benefits	8,577.34	24,849.82	492,033.00	467,183.18
Equipment	-	36,143.00	42,000.00	5,857.00
Supplies & Other	2,267.30	4,113.86	966,334.00	962,220.14
Consulting Services	855.60	855.60	12,000.00	11,144.40
Computers	512.00	5,093.00	12,000.00	6,907.00
TOTAL DIRECT	$ 42,345.63	$ 158,532.79	$ 3,215,021.00	$ 3,056,488.21
Indirect Costs Rate: **10.00%**	4,234.56	15,853.28	321,503.00	305,649.72
TOTAL EXPENDITURES	$ 46,580.19	$ 174,386.07	$ 3,536,524.00	$ 3,362,137.93

STATUS OF REVENUE

Previously Reported	$ 127,805.88
Current Expenditures	$ 46,580.19
Total Expenditures	$ 174,386.07
Total Payments to Date	$ 1,768,262.00
Balance Amount	$ (1,593,875.93)

OUTSTANDING INVOICES

Date	Invoice No.	Amount
		$ -
Total		$ -

CERTIFICATION: BY SIGNING THIS REPORT, I CERTIFY TO THE BEST OF MY KNOWLEDGE AND BELIEF THAT THE REPORT IS TRUE, COMPLETE, AND ACCURATE, AND THE EXPENDITURES, DISBURSEMENTS, AND CASH RECEIPTS ARE FOR THE PURPOSES AND INTENT SET FORTH IN THE AWARD DOCUMENTS. I AM AWARE THAT ANY FALSE, FICTITIOUS, OR FRAUDULENT INFORMATION MAY SUBJECT ME TO CRIMINAL, CIVIL, OR ADMINISTRATIVE PENALTIES (U.S. CODE, TITLE 18, SECTION 1001)

NAME: Marlene Erno, Senior Director of Sponsored Program Administration

for

DATE: 7/11/23